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Interpreting laboratory results

Analytical and biological variation must be taken into account

Millions of laboratory tests are requested each year, and most are used to monitor patients rather than to help diagnosis.[1] Determining whether a change over time is significant may be difficult, and many doctors do not seem to understand the importance of analytical and biological variation.

When a single specimen from a patient is assayed several times identical results are not found every time. The results are distributed normally, and the dispersion—as standard deviation or coefficient of variation—is termed the analytical imprecision.[2] Laboratories undertake quality assurance programmes in which samples with known analyte concentrations are assayed repeatedly. Analytical imprecisions are thus known and should be communicated to all users of the laboratory service.[3]

In addition, the concentration of an analyte from any individual subject varies from day to day. Some analytes have cyclical rhythms that may be daily, monthly, or seasonal.[4] Most, however, have inherent fluctuations, which can be described as random variation around a homoeostatic setting point.[5] This is termed the within subject variation, and many data now exist on a wide range of clinical chemical and haematological analytes.[6] Preanalytical sources of variability —such as changes in the duration of application of a tourniquet—also contribute to the changes seen in laboratory results, but these are minimised by standard collection protocols.

Changes in results are thus caused by analytical imprecision and within subject variation as well as by deterioration or amelioration of the patient's condition. The magnitude of the "critical difference"[7] between results—that is, the change that must occur before significance can be claimed—may be calculated as $K.\sqrt{(CV_a^2+CV_w^2)}$, where K is a factor dependent on the probability level selected, CV_a is the coefficient of analytical variation, and CV_w is the coefficient of within subject variation. (For $p<0{\cdot}05$ the value of K is 2·77.)

The use of this formula may be illustrated by considering a patient whose serum cholesterol concentration has fallen from 7·62 mmol/l to 6·49 mmol/l after three months of dieting. The doctor wants to know whether the diet has been successful or whether the change may be caused simply by analytical and biological variation. When measuring cholesterol concentration a difference of 19% is required for a significant ($p<0{\cdot}05$) change since the ideal coefficient of analytical variation is taken as $\leq 3\%$[8] and the average within subject variation is 6%.[9] Diet has thus not significantly lowered the patient's serum cholesterol concentration.

Average critical differences for other commonly requested analytes are: serum concentrations or activities of sodium 3%, potassium 14%, chloride 4%, urea 30%; creatinine 14%, calcium 5%, albumin 8%, glucose (fasting) 15%, amylase 30%, and carcinoembryonic antigen 69%, blood concentrations of glycated haemoglobin 21%, haemoglobin 8%, erythrocytes 10%, leucocytes 32%, and platelets 25%, and early morning urinary albumin concentration 40%.

These are valid guides to clinical decision making because estimates of within subject variation are similar in health and chronic stable disease and in young and elderly subjects[10] and do not vary among countries.[7] Although not everybody has the same within subject variation for certain analytes, they do for many—which makes the average critical difference useful. Complex mathematical approaches are required to deal with heterogeneity of within subject variation.[11]

Changes in results are often interpreted against empirical criteria—for example, a difference may be considered significant when the test result has doubled or trebled. Moreover, success or failure of treatment is often inferred when the result returns within or remains outside the reference interval (normal range). These practices may be wrong. The within subject variation—the fluctuation around the homoeostatic setting point—is generally less than the between subject variation—the difference between the setting points of individuals.

This considerable individuality means that the range of results that is usual for an individual subject spans only a small part of the reference interval of the population. Results for an individual subject may be unusual for that person but still lie within the interval. Significant changes in results may occur when both lie within the interval, and changes from within to outside or outside to within the interval are not necessarily significant.

The opinions of doctors have been sought on the magnitude of changes in results that prompts clinical action.[12,13] A recent report based on responses to clinical vignettes shows that changes that are needed for action are larger than the critical differences calculated from analytical imprecision and biological variation.[14] This implies that either doctors are unaware of the true differences required for significance or they wish to be more than 95% certain that a change has occurred before taking action. We think it most likely that they are unaware of the true differences. Education of laboratory and clinical staff using simple texts[4] or other interpretative aids is needed. Moreover, laboratories should

consider flagging reports when numerical changes are not significant rather than simply highlighting results outside reference intervals.[15]

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Alcohol and the elderly

Need for greater awareness

Although about 5-12% of men and 1-2% of women in their 60s are problem drinkers,[1] little information is available on the medical problems of elderly dependent drinkers. Furthermore, information on the outcome of treatment is inconclusive because clinical studies have generally included only a few patients.[2] Most of the information that is available stems from North America, and with a few exceptions[3,4] little attention has been paid to the problem in Britain.

The few studies conducted in humans have not shown changes related to age in ethanol metabolism, although blood flow through the liver decreases with age.[5] Body water content declines and body fat content increases with age, and lean body mass decreases by about 10% between the ages of 20 and 70. Combined reductions of body water content and lean body mass probably account for higher blood alcohol concentrations in the elderly than in younger people after a standard dose.[6]

Some areas of the brain are more vulnerable to alcohol than others, which is particularly important in older people. The basal ganglia, hippocampus, reticular activating system, and neocortex undergo faster neuronal loss with aging than other regions of the brain, these changes resulting in impaired cognition and motor skills.[6] Probably at least 10% of patients presenting with dementia have alcohol related brain disease.

In some elderly people alcohol misuse has been a longstanding problem, but bereavement, retirement, loneliness, or boredom may lead to reactive depression with subsequent heavy drinking in others.[4] Elderly alcohol misusers are more likely than younger misusers to hide their drinking, and they have a greater tendency to drink daily rather than to binge.[7] Between 5% and 15% of elderly people with alcohol problems suffer from a pre-existing depressive disorder,[8] and alcohol is important in about a third of suicides in elderly people.[9]

In medical terms non-specific presentations of alcohol misuse among the elderly are the rule. Poor hygiene, myopathy, accidental hypothermia, osteoporosis, unexplained hyperuricaemia, hypoglycaemia, and hypertriglyceridaemia may be caused or exacerbated by alcohol misuse in the elderly.[10] Alcohol may have an additive sedative effect when combined with diazepam, amitriptyline, barbiturates, and chloral hydrate; serum concentrations of the drugs are increased because alcohol reduces their metabolism. Conversely, metabolism of barbiturates, tolbutamide, phenytoin, and warfarin may be increased because of enzyme induction in the liver.[11] Dependence on alcohol and one or more psychotropic drugs was found in 14% of elderly patients in one study.[12]

Medical problems tend to be more prominent in elderly drinkers than in young drinkers, particularly if they began drinking at a younger age.[13] Cirrhosis of the liver, peripheral neuropathy, and cerebellar degeneration are common, and a third of patients in a series of elderly patients had some form of alcoholic liver disease.[13] Alcohol may provoke or exacerbate parkinsonism in older patients,[14] and delirium tremens is associated with a higher mortality in elderly people.[15]

A study in Baltimore showed that the age specific incidence of cirrhosis in white men living in urban areas was the highest in the seventh decade[16] whereas in Europe a fifth of patients with alcoholic liver disease were over 60 at presentation.[17] Evidence of severe liver disease was more prominent among the very elderly, and nearly a third presented with symptoms not directly related to liver disease, the commonest being dizziness and falling.[18] Prognosis was age related: mortality after one year was 50% among those over 60 with cirrhosis and 7% in those under 60.[18] A smaller community based study showed that 13% of subjects over 60 were drinking enough to put them at risk of alcoholic liver disease.[3]

Musculoskeletal pain, insomnia, loss of libido, depression, and anxiety are recognised complications of heavy drinking but are common complaints among the elderly anyway. Ironically, elderly alcohol misusers may cite these reasons to justify their heavy drinking when alcohol is the cause.[19]

A history of alcohol use should be obtained routinely from all patients. Blood alcohol concentrations fall on average by 15 mg/100 ml/hour[20] so tests carried out after some delay may be misleading. The clinical threshold for alcohol dependence should be set much lower in the elderly than in the young because of their particular vulnerability to the toxic effects of alcohol.

Treatment must begin with detoxification and be followed by emphasis on abstinence and education about the dangers of alcohol and polysubstance misuse. As a rule the elderly should not be given benzodiazepines to prevent withdrawal symptoms as these may produce delirium, but when necessary drugs with a short half life—such as lorazepam or chlormethiazole—